Malignancies in Fibrous Dysplasia

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Background. **Malignancies in fibrous dysplasia are rare. Most cases have been published as single case reports. The role of radiation therapy in the occurrence of sarcoma in fibrous dysplasia is still controversial.**

Methods. **The Mayo Clinic files were reviewed, including Mayo Clinic cases and consultation cases, to collect all cases of sarcomas arising in fibrous dysplasia.**

Results. **Among 1122 cases with a histologic diagnosis of fibrous dysplasia, 28 cases of sarcoma were found. These 28 cases included 16 Mayo Clinic cases and 12 consultation cases. The sarcomas occurred in 19 cases of monostotic fibrous dysplasia and 9 cases of polyostotic disease (only 1 of Albright's syndrome). The most common histotype was osteosarcoma (19 cases), followed by fibrosarcoma (5 cases), chondrosarcoma (3 cases), and malignant fibrohistiocytoma (1 case). Of the 28 patients, 13 (46%) had received radiation therapy before the sarcoma developed. Most of these sarcomas occurred in the craniofacial bones (13 cases) or in the proximal femur (7 cases), followed by the humerus, pelvis, tibia, and scapula.**

Conclusions. **Prognosis was poor. Sarcomas may arise with or without radiation. Early diagnosis and adequate treatment may lead to improved prognosis.** ***Cancer*** **1994; 73:1411–24.**

Key words: sarcomas in fibrous dysplasia, fibrous dysplasia, secondary sarcomas, radioinduced sarcomas.

Malignancies in fibrous dysplasia are rare. They can occur in monostotic and polyostotic fibrous dysplasia[1-4]; their frequency ranges from 0.5% (in monostotic disease) to 4% in Albright's syndrome.[1,5]

The first documented case was reported by Coley and Stewart in 1945.[6] In 1964, Schwartz and Alpert[1] reported two personal cases and 26 documented cases collected in the literature. Most of the descriptions of sarcomas in fibrous dysplasia that are in the literature are single case reports or reports of a few cases.[7-19] The largest series, which includes 15 cases, is that from Memorial Sloan-Kettering Cancer Center, New York.[2,20] In 1988, Yabut and coworkers[4] reported a new case and found 83 cases in a careful review of the literature. The most common of the malignancies was osteosarcoma, followed by fibrosarcoma and chondrosarcoma. The possibility of sarcomatous change in fibrous dysplasia without prior irradiation seems well established, as verified by several reports of documented cases.[2,4,11] The role of radiation therapy in the occurrence of sarcoma in fibrous dysplasia is still controversial.[4,7,21] In Huvos' series,[20] only 1 of 15 patients with sarcomas in fibrous dysplasia had received radiation therapy. In the review of the literature by Yabut and coworkers,[4] 23 patients had received radiation therapy, 46 had not had prior irradiation, and 14 did not have information available. The purpose of the current study was to review and report our experience with malignancies in fibrous dysplasia.

Materials and Methods

We included only cases with histologic evidence of both fibrous dysplasia and sarcoma, with the exception of cases of polyostotic fibrous dysplasia, in which, according to Schwartz and Alpert's criteria,[1] the diagnosis of fibrous dysplasia was accepted if there were characteristic clinical and radiographic features.

To collect the cases, we reviewed the Mayo Clinic files and our consultation files for the following diagnoses: fibrous dysplasias associated with osteosarcoma, fibrosarcoma, chondrosarcoma, and malignant fibrous histiocytoma. This review yielded 33 cases. Five cases were excluded. One patient with a small cell fibrosarcoma of the femur and radiographic features of fibrous dysplasia in the ribs was excluded because there was no conclusive evidence for the diagnosis of fibrous dysplasia. One patient with a periosteal chondroblastic osteosarcoma of the tibia and fibrous dysplasia of the skull was excluded because the coexistence of the two lesions

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in the same patient was thought to be coincidental. A third patient with an osteosarcoma of the jaws was excluded because the review of the histologic slides did not show conclusive evidence of fibrous dysplasia. In a fourth patient (seen in consultation in 1961), a diagnosis of osteosarcoma of the proximal humerus and fibrous dysplasia was changed to fibrocartilaginous mesenchymoma with low-grade malignancy[22]; this patient was therefore excluded from our series. The fifth patient had coexisting features of fibrous dysplasia and Paget's disease of the jaws and had development of an osteosarcoma in the same site[23]; this patient was excluded because of the possibility of osteosarcoma arising in Paget's disease.

Our series thus includes 28 patients with sarcoma and fibrous dysplasia: 16 Mayo Clinic cases and 12 consultation cases. Histologic slides from all 28 cases were available for review. Pertinent clinical information was obtained from the charts and letters of consulting pathologists, and follow-up information was gained from the charts, the patients (by questionnaires), or the consulting pathologists.

Clinical Data

A summary of the pertinent clinical data for the 28 patients is shown in Table 1. Some of these cases have already been reported.[7,8,23–25] The ages of the patients (12 males and 16 females) at the time of initial presentation of fibrous dysplasia ranged from 2 to 61 years. Their ages at the time of initial presentation of sarcoma ranged from 18 to 66 years. Most of the patients had the fibrous dysplasia diagnosed some years before the diagnosis of sarcoma (range, 1–52 years). In only four cases (three consultation cases and one Mayo Clinic case) was the diagnosis of fibrous dysplasia established concurrently with that of sarcoma. When sarcoma was diagnosed, two patients were in the second decade of life, five in the third, three in the fourth, seven in the fifth, four in the sixth, and seven in the seventh.

According to Schwartz and Alpert's criteria,[1] for the purpose of the current study craniofacial fibrous dysplasia was considered monostotic, because craniofacial fibrous dysplasia uncommonly affects just one facial bone and it is difficult to state whether it primarily affected multiple bones or simply extended from one to another. Of the 28 patients, 19 (11 Mayo Clinic cases and 8 consultation cases) had monostotic fibrous dysplasia, and 9 (5 Mayo Clinic cases and 4 consultation cases) had polyostotic disease.

The sites involved by fibrous dysplasia and the sites of sarcoma are reported in Table 1 and Figure 1. Most of the sarcomas occurred in the craniofacial bones (13 cases) or in the proximal femur (7 cases); other sites were the humerus (3 cases), pelvis (2 cases), tibia (2 cases), and scapula (1 case). In all patients, the sarcoma occurred in a bone affected by fibrous dysplasia. One patient (Patient 13, Table 1) with monostotic fibrous dysplasia of the humerus and osteosarcoma had a chondrosarcoma of the proximal femur (diagnosed and treated elsewhere 27 years after forequarter amputation for osteosarcoma). No other patients had multiple tumors.

Regarding the symptoms of fibrous dysplasia, only one patient (Patient 10) had Albright's syndrome. Five patients' conditions were asymptomatic; one of these was diagnosed as having fibrous dysplasia, and in the other four the fibrous dysplasia remained undiagnosed until the discovery of the sarcoma. The symptoms of fibrous dysplasia in the remaining patients were variable and generally of long duration; they included pain, swelling, deformities, and pathologic fractures. The symptoms of the sarcoma were mostly pain and swelling, usually developing rapidly.

Radiation had been given as a treatment of the fibrous dysplasia in 10 of the patients and as a treatment of conditions other than fibrous dysplasia in 3 patients (acne in 2, frozen shoulder in 1). In all of these 13 patients, the sarcoma developed in the field of prior irradiation. The interval between radiation therapy and the occurrence of sarcoma ranged from 3 to 52 years (mean, 19 years). This interval was unknown in one patient (Patient 15, Table 1), who was reported to have had radiation therapy for facial acne "when young." In most of the cases, the doses of the radiation given were unknown.

Radiographic Appearance

Radiographs were available for review in only three Mayo Clinic patients and four consultation patients. In the remaining patients, the radiographs had been discarded or returned to the source of the referral and could not be obtained. In four of the seven patients with radiographs, the sarcoma was associated with fibrous dysplasia involving the proximal half of the femur. In general, the sarcoma produced an area of poorly marginated, purely osteolytic destruction associated with radiographically typical fibrous dysplasia (Fig. 2). In four of the sarcomas, the overlying cortex was destroyed by the osteolytic tumor, which extended into the adjacent soft tissue. The cortex was eroded and very thin but not disrupted in the other three cases (Fig. 3). Only one sarcoma was associated with radiographically visible mineral (Fig. 4). Periosteal reaction was not prominent. There was slight periosteal reaction associated with three of the sarcomas and no periosteal reaction in the other four. Pathologic fracture occurred

Table 1. Clinical Data for 28 Patients With Sarcoma in Fibrous Dysplasia*

		Fibrous dysplasia						Sarcoma						
Patient no.	Sex	Age at onset (yr)	Type	Bones affected	Symptoms	Treatment	Radiation therapy	Age at onset (yr)	Bones affected	Symptoms	Histologic diagnosis	Treatment	Further treatment	Follow-up (yr + mo)
1	M	3	M	Maxilla	Swelling	Radium (1919), excision (1919), radium (1920)	Yes (two cycles)	46	Maxilla	Pain, swelling	Grade 3 fibroblastic OGS	10/62, resection	11/63, exenteration orbit; 2/65, excision; 9/65, excision	5 + 2 (12/67), died of tumor
2	M	8	M	Maxilla	Pathologic fracture (1 yr later), swelling	Radiation (1930, 1938)	Yes (5700 R)	18	Maxilla	Pain, eye compression	Grade 3 osteoblastic OGS	10/38, biopsy and radiation (removal not possible)		4 + 11 (9/42), died of tumor
3	F	7	P	Humerus, radius, hand, pelvis, femur	Pathologic fractures	Splints, biopsy, radiation (1939)	Yes (two cycles)	40	Humerus	Pain, swelling	Grade 2 chondrosarcoma	1/72, shoulder disarticulation		5 + 7 (8/77), died with lung/liver metastasis
4	M	11	P	Femur, ilium	Limping, pain	Radiation (1941)	Yes	53	Proximal femur	Pain	Grade 3 fibrosarcoma	7/61, hindquarter amputation	9/62, excision of recurrence	1 + 11 (6/73), died with recurrence
5	F	5	M	Maxilla	Pain, swelling	Excision (1928, 1931); radiation (1936)	Yes (daily for 3 mo)	24	Maxilla	Pain, swelling, eye dislocation	Grade 3 chondroblastic OGS	8/45, biopsy (not operable)		0 + 4 (12/45), died of tumor
6	M	23	M	Mandible	Swelling	Excision (1948)	Yes (1946), 750 R for acne	25	Mandible	Swelling	Grade 3 fibrosarcoma	6/50, excision	8/50, excision of recurrence; 12/50, radiation for recurrence	1 + 2 (8/51), died with bone and lung metastasis
7	M	8	M	Mandible, maxilla	Swelling	Excision (1930), radiation (1930), excision (1935)	Yes (6070 R)	35	Mandible, maxilla	Swelling	Grade 3 osteoblastic OGS	11/56, biopsy, radiation (4200 R)	3/57, excision; 12/64, radiation (3000 R)	9 + 2 (1/66), died of tumor
8	F	14	M	Skull	Swelling, pain	Radiation (1936), excision (1940)	Yes	66	Skull	Swelling	Grade 3 osteoblastic OGS	12/88, embolization and excision	6/90, excision of recurrence; 10/90, excision of recurrence	2 + 8 (8/91), died of tumor
9	M	45	M	Scapula	Pain	Biopsy (1960)	Yes (1959), for frozen shoulder	49	Scapula	Swelling, pain	Grade 3 fibroblastic OGS	3/62, scapulectomy	12/62, forequarter amputation; 1/63, chemotherapy/lung metastasis; 7/65, left pneumonectomy	4 + 2 (5/66), died with lung metastasis

Table 1. (*Continued*)

Patient no.	Sex	Fibrous dysplasia						Sarcoma						
		Age at onset (yr)	*Type*	*Bones affected*	*Symptoms*	*Treatment*	*Radiation therapy*	*Age at onset (yr)*	*Bones affected*	*Symptoms*	*Histologic diagnosis*	*Treatment*	*Further treatment*	*Follow-up (yr + mo)*
10	F	7	P	Tibia, femur, radius, ribs, pelvis	Precocious puberty, pigmented skin areas, pathologic fractures, hypertension (Albright's syndrome)	Orthopedic treatment of fractures	No	40	Ilium	Swelling, pain	Grade 4 fibroblastic OGS	8/71, biopsy (not operable); radiation (6300 R)		0 + 5 (1/72), died with lung metastasis
11	F	19	M	Mandible	Swelling	Excision (1921, 1935), excision, radiation (1951)	Yes	52	Mandible	Swelling, pain	Grade 2 chondroblastic OGS	6/54, biopsy (not operable), radiation recommended		Lost to F/U
12	F	58	M	Skull	Headache, diplopia, paralysis of cranial nerve VI	Excision (1968)	No	60	Skull (sphenoid)	Headache, pain	Grade 4 fibrosarcoma	2/69, excision and radiation (5000 R)		0 + 5 (7/69), died of tumor
13	M	25	M	Proximal humerus	Pain, pathologic fracture	Excision (1950), grafts	No	27	Proximal humerus	Pathologic fracture	Grade 3 chondroblastic OGS	10/51, forequarter amputation	7/78, hindquarter amputation, radiation (for chondrosarcoma, proximal femur)	18 + 0 (1979), died with lung metastasis
14	M	6	P	Skull, mandible, femurs, humeri, pelvis, fibula, hand	Deformities	Multiple procedures for deformities	No	15	Proximal femur	Pathologic fracture	Clear cell chondrosarcoma	10/61, hip disarticulation	10/65, excision of recurrence, 1/67, excision of recurrence 9/67, hindquarter amputation, chemotherapy	19 + 3 (1/81), died with lung metastasis
15	F	26	M	Maxilla	Swelling, pathologic fracture	Excision (1964)	Yes, for acne	32	Maxilla	Swelling	Grade 3 fibroblastic OGS	12/66, resection and exenteration, orbit	Several reconstructive procedures	25 + 6 (6/92), NED
16	F	52	P	Femurs, pelvis			No	52	Hemipelvis	Pain, swelling	Grade 2 chondrosarcoma	4/63, hindquarter amputation	2/64, excision of recurrence; 4/64, excision of recurrence and radiation (6500 R)	3 + 6 (10/66), died of tumor
17	M	Known to have since young	P	Femur fibula			No	64	Proximal femur	Pain, stress fracture	Grade 3 fibroblastic OGS	5/87, hip disarticulation and chemotherapy		4 + 10 (9/22), NED

Table 1. (*Continued*)

		Fibrous dysplasia						Sarcoma						
Patient no.	Sex	*Age at onset (yr)*	*Type*	*Bones affected*	*Symptoms*	*Treatment*	*Radiation therapy*	*Age at onset (yr)*	*Bones affected*	*Symptoms*	*Histologic diagnosis*	*Treatment*	*Further treatment*	*Follow-up (yr + mo)*
18	M	55	M	Proximal femur	Pain	Biopsy (1981)	No	61	Proximal femur	Pain, swelling	Grade 3 osteoblastic OGS	12/87, resection	5/91, internal hemipelvectomy (for recurrence)	4 + 5 (5/92), alive with recurrence
19	F	43	M	Proximal femur	Pain	Curettage (1991)	No	44	Proximal femur	Swelling	Grade 2 fibroblastic OGS	3/92, resection		0 + 3 (6/92), NED
20	M	57	M	Proximal femur			No	57	Proximal femur	Pain	Grade 4 fibroblastic OGS	11/91, resection		0 + 6 (5/92), alive with metastasis and recurrence
21	M	15	P	Femurs, tibia, fibulas	Pathologic fractures	Osteotomies (1982)	No	41	Tibia	Swelling	Grade 2 fibroblastic OGS	7/83, above-knee amputation and chemotherapy	9/83, excision of myxoma	1 + 0 (7/84), NED; since lost to F/U
22	F	38	M	Skull			No	38	Skull (frontal)	Diplopia, eye dislocation	Grade 3 fibroblastic OGS	11/79, excision		Lost to F/U
23	F	35	M	Maxilla	Swelling	Biopsies (1945, 1949) Radiation (1949)	Yes	66	Maxilla	Swelling	Grade 3 fibroblastic OGS	2/76, resection		15 + 3 (5/91), NED
24	F	9	M	Maxilla	Swelling	Biopsy (1962), cosmetic surgery	No	17	Maxilla	Swelling, eye dislocation	Grade 3 chondroblastic OGS	5/70, excision		0 + 8 (1/71), died with recurrence
25	F	61	M	Skull			No	61	Skull	Headache, swelling	Grade 4 fibroblastic OGS	1/80, resection and radiation (5000 R)		9 + 0 (1989), NED
26	F	2	P	Tibia, femur	Deformities	Biopsy (1969)	No	24	Proximal femur	Pain	Grade 3 fibrosarcoma	2/73, biopsy	?	?
27	F	16	M	Tibia	Pain	Biopsy (1955), radiation (1956)	Yes	21	Tibia	Pain, swelling	Grade 3 fibrosarcoma	2/60, above knee amputation		? bone metastasis (spine)
28	F	21	P	Humeri, ulna	Pain		No	66	Distal humerus	Pain, swelling	Grade 4 MFH	7/83, shoulder disarticulation and chemotherapy		7 + 0 (1990), NED; since lost to F/U

M: monostotic; P: polyostotic; OGS: osteogenic sarcoma; MFH: malignant fibrous histiocytoma; F/U: follow up; NED: no evidence of disease.

* All patients except two (patients 13 and 28) had histologic evidence of fibrous dysplasia.

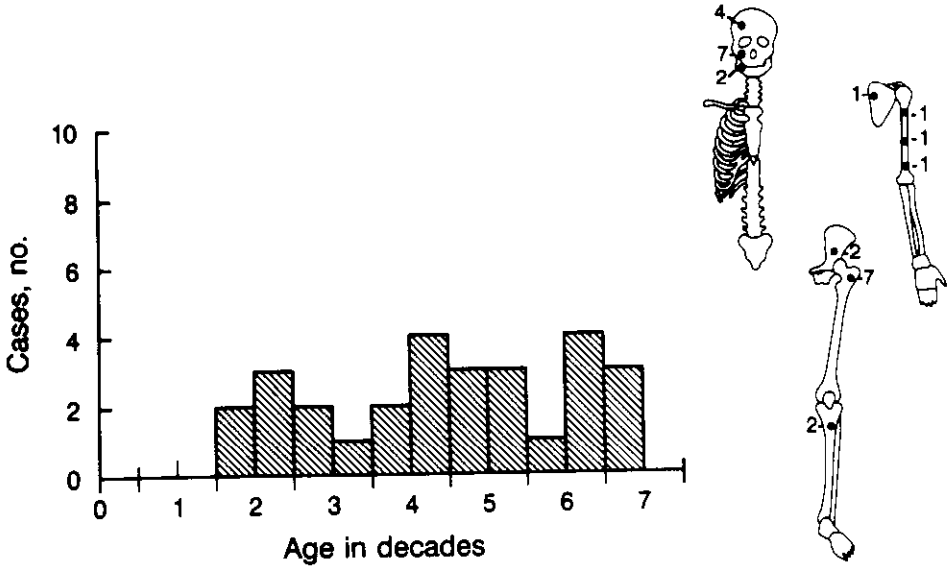

Figure 1. Distribution of age and sites of lesions in 28 patients with sarcoma in fibrous dysplasia.

through one sarcoma (Fig. 5). In addition, in one unusual case, the radiographic findings were typical of osteogenesis imperfecta cystica and the histologic findings were typical of fibrous dysplasia (Fig. 6). The associated malignancy was the only clear cell chondrosarcoma in this series.

Microscopic Appearance

There was histologic confirmation of fibrous dysplasia in 26 of the cases; 2 of the cases (Patients 10 and 28, Table 1) lacked histologic evidence but were included in the series, according to the criteria mentioned above.

Figure 2. (Left) Typical fibrous dysplasia involving the proximal femur. (Right) Six years later, osteolytic destruction due to osteosarcoma has developed at the superior aspect of fibrous dysplasia.

Figure 3. Osteolytic destruction involving the proximal right femur by fibrosarcoma associated with fibrous dysplasia. The cortex is eroded and very thin. Fibrous dysplasia also involves the right ilium.

Both patients had well-established diagnoses of polyostotic fibrous dysplasia with a long clinical course and typical radiographic features. One of these two patients (Patient 10) had Albright's syndrome with polyostotic fibrous dysplasia, skin pigmentation, and precocious puberty.[5]

We were unable to review the slides of fibrous dysplasia in one other case (Patient 3, Table 1). The slides had been reviewed previously by Dr. D. C. Dahlin (Emeritus Consultant, Section of Surgical Pathology, Mayo Clinic and Mayo Foundation), who had confirmed the diagnosis of fibrous dysplasia with cartilage. All other cases showed typical fibrous dysplasia, including the one case in which the radiographs were atypical (Fig. 7). Fibrous dysplasia was identified in slides obtained at the time of operation for the sarcoma in 8 cases (Fig. 8), from slides obtained before surgical procedures in 8, and from slides obtained both before and after operation in 10. The second case of chondrosarcoma was not associated with fibrochondrodysplasia.

The slides from all the sarcomas were reviewed. There were 19 osteosarcomas and 1 malignant fibrous histiocytoma. Eleven of the osteosarcomas were fibroblastic (Fig. 9), and four each were chondroblastic and osteoblastic. Of the 19 osteosarcomas, 3 were Grade 4, 13 were Grade 3, and 3 were Grade 2 (Fig. 10). Five of the spindle cell sarcomas did not show any matrix and were considered fibrosarcomas. Four of these were Grade 3 and one was Grade 4.

Three tumors were considered Grade 2 chondrosarcomas (Fig. 11). The one clear cell chondrosarcoma (Fig. 12) had foci of conventional chondrosarcoma.

ure 4. (Left) Typical polyostotic fibrous dysplasia involving the ilium and proximal femur, bilaterally, in a young female with Albright's ndrome. (Right) Four years later, osteosarcoma had developed in the left ilium and acetabulum. Note osseous destruction and slightly mineralized large soft tissue mass.

Figure 5. Pathologic fracture through osteosarcoma involving the proximal left femur. Remaining fibrous dysplasia is seen just distal to lytic sarcoma.

One tumor had very pleomorphic nuclei and giant cells and was considered a Grade 4 malignant fibrous histiocytoma.

Treatment

Patients were divided into four groups according to the treatment of the sarcoma: excision, resection, amputation, and radiation therapy. Excision was defined as complete or incomplete removal of the tumor without surrounding normal tissue; therefore, in this group the margins were never oncologically adequate, being intralesional in most of the cases and never better than marginal.[26] Resection was considered a procedure that attempted to remove the tumor completely with a wide margin.[26] For one of our consultation cases (Patient 26, Table 1), we did not have any information on treatment or follow-up.

Five patients underwent excision as initial treatment of the sarcoma, and eight patients underwent resection as initial treatment. In addition, nine patients had an amputation. Information on further relapses and treatment of these patients is reported in Table 1. Radiation therapy was given as initial treatment in three patients. In two other cases (Patients 5 and 11),

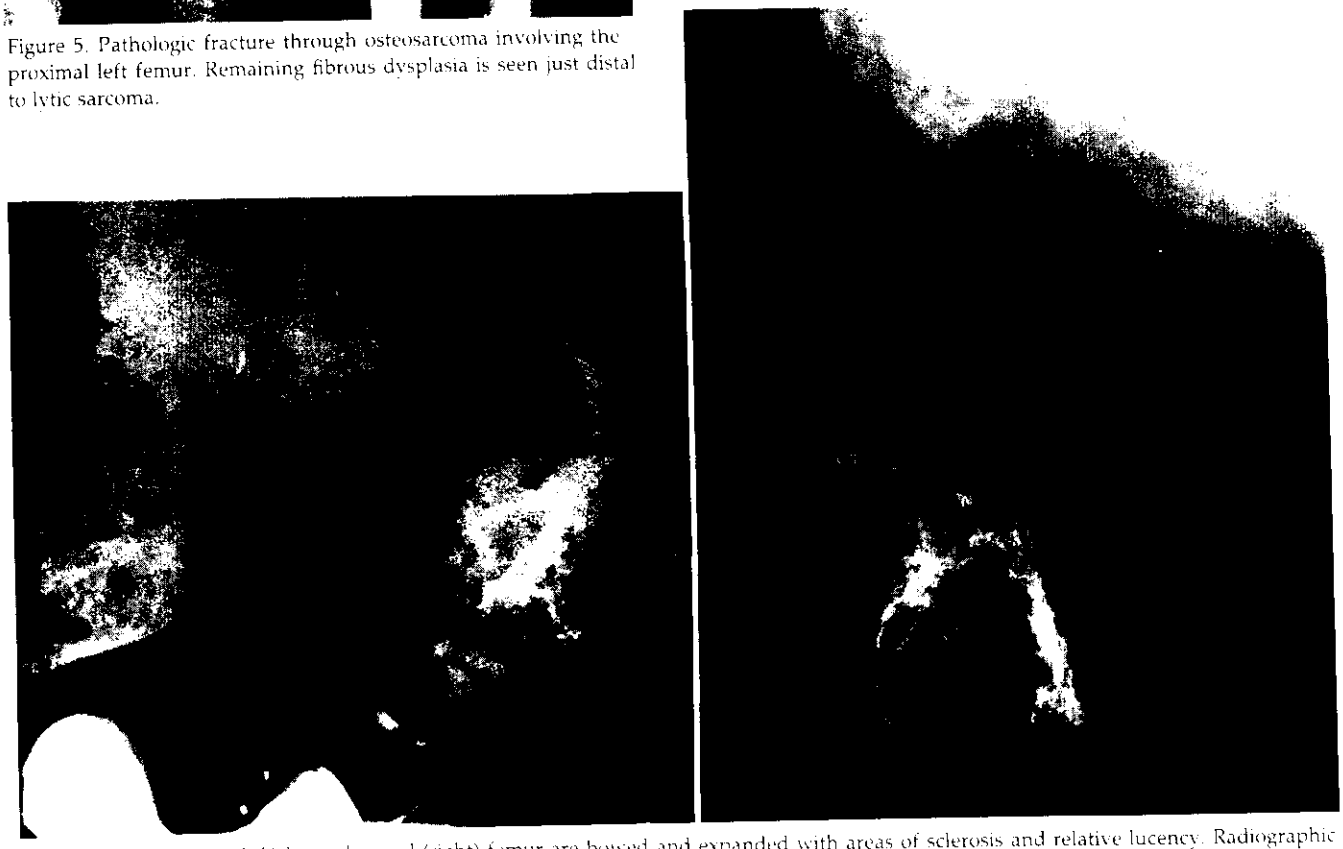

Figure 6. Bones of the (left) lower leg and (right) femur are bowed and expanded with areas of sclerosis and relative lucency. Radiographic findings are typical of osteogenesis imperfecta cystica. Histologic appearance was typical of fibrous dysplasia. Associated clear cell chondrosarcoma has destroyed most of the proximal femur.

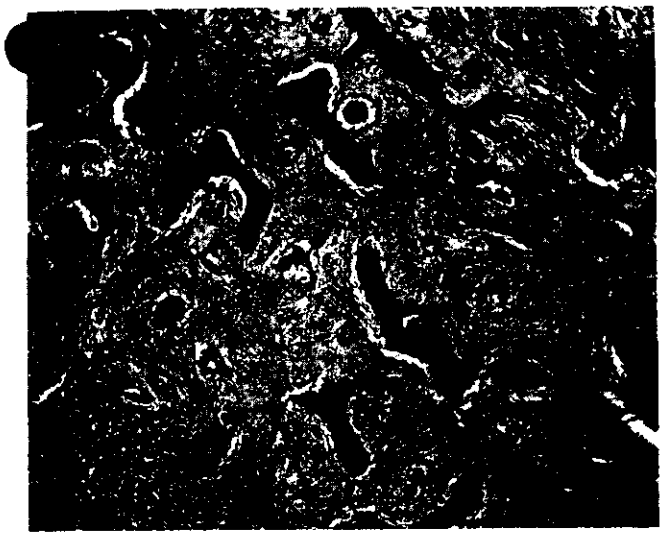

Figure 7. Irregular bone and spindle cell proliferation of the femur consistent with fibrous dysplasia. (H & E, original magnification ×160).

radiation therapy was recommended. It was not feasible in Patient 5 because of active actinodermatitis. Moreover, radiation therapy was given as adjuvant treatment in Patients 12 and 25 and as a treatment of recurrent tumor in four patients (Patients 6, 7, 13, and 16).

Follow-Up

Of the 28 patients, 15 had died of tumor, 4 were lost to follow-up, and 9 were alive (2 were alive with disease and for 3 others the duration of follow-up was short). Only four patients were alive without disease for more than 5 years. Of these four patients, two had had prior radiation and two had not. Two tumors involved the maxilla, one the skull, and one the humerus.

Discussion

The occurrence of sarcoma in fibrous dysplasia is well established in the literature, both in monostotic and polyostotic disease.[10,20,21,27–32] Sarcomas in fibrous dysplasia have been reported after radiation therapy[1,3,7,21,27] and without prior irradiation.[1–4,11,20,28,30,31] The frequency of sarcoma in fibrous dysplasia as reported in the literature ranges from 0.4%[4] to 6.7%.[33] It is, however, generally accepted that the actual frequency is less than 1%.[3,4,20,27] Schwartz and Alpert[1] reported a frequency of sarcoma in fibrous dysplasia of 0.5% (confirmed by Taconis[17]), but a higher frequency of 4% in Albright's syndrome.

In the Mayo Clinic's files, there are more than 1122 cases with a histologic diagnosis of fibrous dysplasia (approximately 12% are polyostotic); from these, 28 cases of sarcoma were identified (2.5%). This high percentage of malignancies in fibrous dysplasia compared with that in other reported series[11] may be explained by the referral of atypical cases to major centers. In the current series, 19 sarcomas were in monostotic fibrous dysplasia and 9 were in polyostotic disease. In only one case was a sarcoma observed in a patient with Albright's syndrome. The higher number of malignancies in monostotic disease is probably explained by the remarkably higher number of monostotic than polyostotic fibrous dysplasias, and it is similar to the data already reported in the literature.[4,20]

The sites involved by the sarcoma in the current series seem to correspond with those described in the review of the literature by Yabut and coworkers,[4] and the distribution reflects the frequency of occurrence of fibrous dysplasia in the skeleton.[21] Concerning the histotypes of sarcomas observed, the most common was the osteogenic sarcoma (19 cases), followed by fibrosarcoma (5 cases), chondrosarcoma (3 cases), and malignant fibrohistiocytoma (1 case). These are comparable to the histotypes observed by Yabut and coworkers[4] in 83 cases from the literature: 40 osteosarcomas, 22 fibrosarcomas, 11 chondrosarcomas, and 10 other sarcomas.

One of the three chondrosarcomas was a clear cell chondrosarcoma in a patient with atypical polyostotic fibrous dysplasia. This patient has already been described in a previous report.[24] The occurrence of desmoplastic fibroma in a bone affected by fibrous dysplasia has been reported previously.[34] In the Mayo Clinic files, we did not find any similar case. Concerning the grading of these sarcomas,[35] most of the patients had high-grade sarcoma, and only six were low-grade (one clear cell chondrosarcoma, two Grade 2 chondrosarcomas, three Grade 2 osteosarcomas). These low-grade sarcomas included two malignancies after irradiation (Patients 3 and 11). One of these two cases (Patient 3) was a Grade 2 chondrosarcoma with a clear extension in the soft tissues through the bony cortex. The second case (Patient 11) was a Grade 2 chondroblastic osteosarcoma that had only a biopsy because removal of the tumor was not feasible; therefore, an insufficient sampling of tissue may be the cause of underestimation of grading. Of our 28 patients, 16 were female and 12 were male. Sarcomas in fibrous dysplasia do not seem to predominate in one sex, in agreement with the literature.[2–4]

Regarding age, in our series almost all ages were affected (range, 17–66 years), but most of the patients were beyond the third decade at the time of sarcoma occurrence. This age distribution is consistent with the data from the review by Yabut and coworkers[4] but is older than that in the Memorial Sloan-Kettering series.[2] The age of the patients was considered in the two

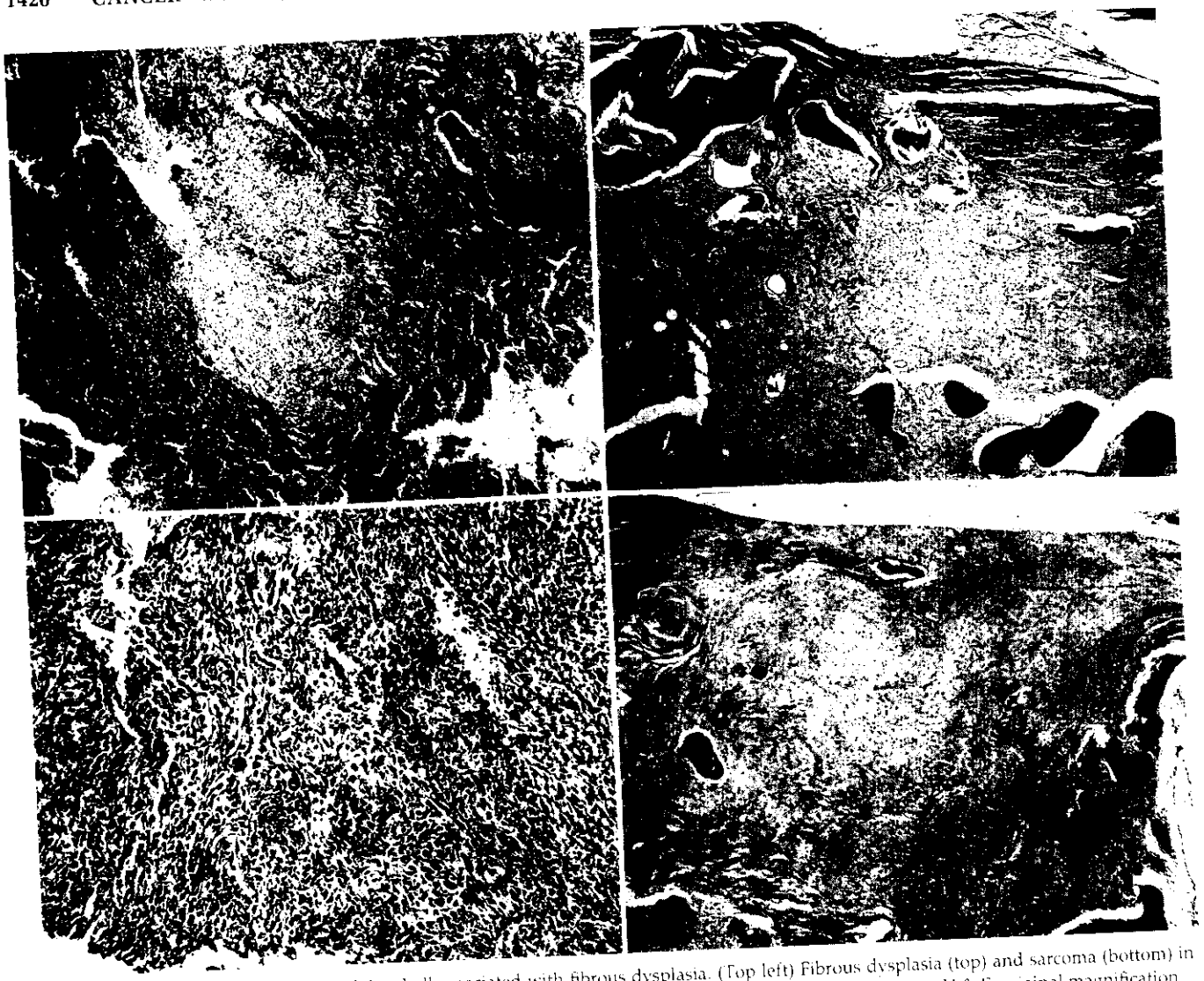

Figure 8. Fibroblastic osteosarcoma of the skull associated with fibrous dysplasia. (Top left) Fibrous dysplasia (top) and sarcoma (bottom) in the same field (H & E, original magnification ×64). (Top right) Appearance of area of typical fibrous dysplasia (H & E, original magnification ×64). (Bottom left) Higher-power appearance of spindle cell sarcoma. Fine lacelike osteoid is in the top left corner (H & E, original magnification ×160). (Bottom right) A different area of fibrous dysplasia with myxoid change in the same lesion (H & E, original magnification ×64).

groups with monostotic and polyostotic disease: the ages ranged from 17 to 66 years (mean, 43 years) in patients with sarcoma in monostotic fibrous dysplasia and from 24 to 64 years (mean, 44 years) in patients with sarcoma in polyostotic fibrous dysplasia. Similarly, no major differences were found between the ages of patients who had sarcoma after prior irradiation (mean, 40 years; range, 18–66 years) and those who had not received radiation therapy (mean, 46 years; range, 17–66 years). According to Huvos and coworkers,[2] we divided our patients into two groups: 24 with a known diagnosis of fibrous dysplasia in whom the sarcoma was diagnosed later (mean interval, 21 years) and 4 patients in whom fibrous dysplasia and sarcoma were diagnosed simultaneously. In the latter group, the mean age was 42 years (range, 17–66 years), whereas in the former group the mean age was 52 years (range, 38–61 years). These data do not allow any valid consideration because of the small number in the latter group. The age in both groups is older than that in the series from Memorial Sloan-Kettering.[2]

The importance of radiation therapy in the occurrence of sarcoma in fibrous dysplasia has been emphasized by some authors[7,21] and denied by others.[2,20] Schwartz and Alpert,[1] on the basis of their review, questioned whether ionizing radiation could enhance the natural tendency of fibrous dysplasia to undergo sarcomatous change. In 1948, Cahan and coworkers[36] pro-

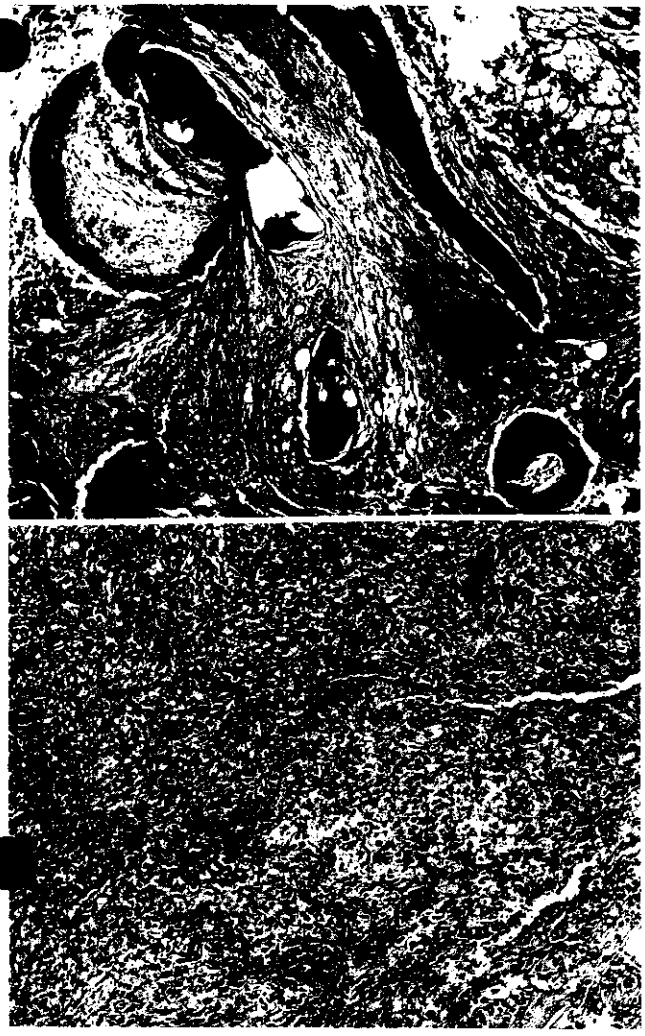

Figure 9. (Top) Typical fibrous dysplasia in the proximal femur (H & E, original magnification ×100). (Bottom) Another area in the biopsy showing Grade 4 fibroblastic osteosarcoma (H & E, original magnification ×160).

posed the following criteria for the diagnosis of postradiation sarcoma of bone:

1. There must have been microscopic or radiographic evidence of the nonmalignant nature of the initial bone condition.
2. Irradiation must have been given and the sarcoma that subsequently developed must have arisen in the area included within the radiotherapeutic beam.
3. A relatively long, asymptomatic latent period must have elapsed after irradiation before the clinical appearance of the bone sarcoma (they suggested 5 years).
4. All sarcomas must have been proved histologically.

Arlen and associates,[37] in 1971, modified the first criterion to include malignant tumors devoid of osteoblastic activity, such as Ewing's sarcoma and malignant lymphoma of bone. They also proposed that a latent period of 3–4 years is more realistic.

Huvos and associates (including Cahan),[38] in 1985, modified the criteria of Cahan et al.[36] as follows:

1. The patient received irradiation.
2. The neoplasm occurred in the radiation field.
3. A latent period of some years had elapsed.
4. There was histologic or radiographic evidence for the preexistent osseous condition, if it was present, in addition to microscopic proof for a sarcoma.

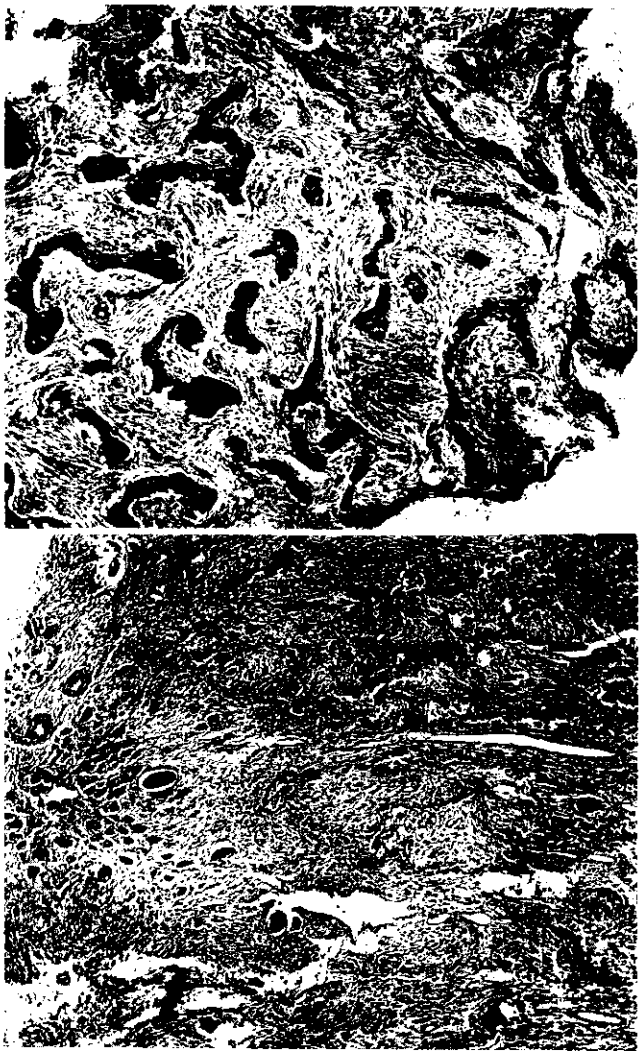

Figure 10. (Top) Area of typical fibrous dysplasia in the proximal femur (H & E, original magnification ×100). (Bottom) Different area showing matrix-producing neoplasm invading skeletal muscle (right). The tumor is less cellular than conventional osteosarcoma (H & E, original magnification × 100).

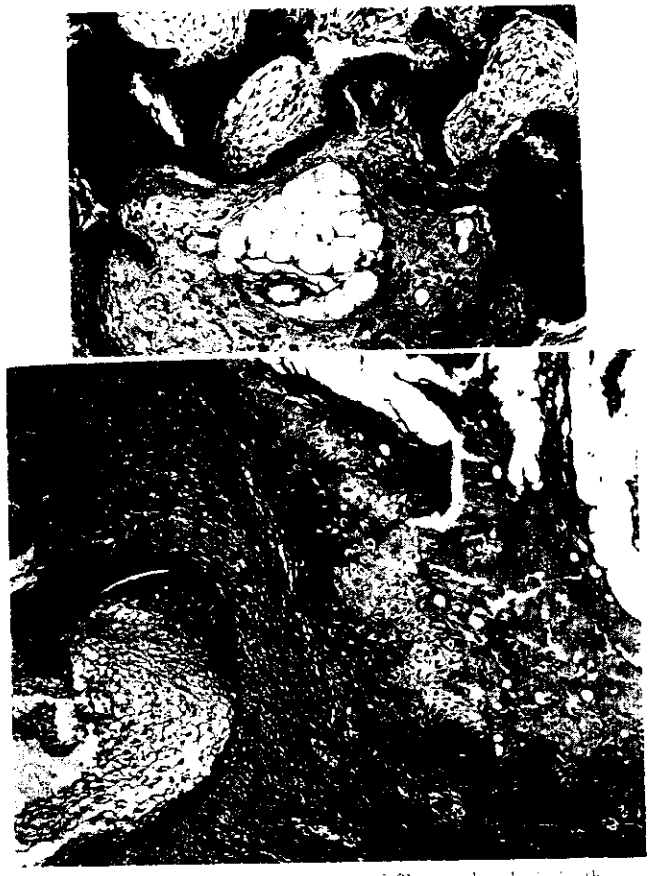

Figure 11. (Top) Typical appearance of fibrous dysplasia in the femur of a 52-year-old woman (H & E, original magnification ×100). (Bottom) Hypercellular islands of cartilage with myxoid change from the ilium (H & E, original magnification ×100).

According to these criteria, 13 of our cases have to be regarded as radiation-induced sarcoma[39] not necessarily related to fibrous dysplasia. This opinion is in accordance with that expressed by Yabut and coworkers[4] for 23 sarcomas in their review that had received irradiation. Therefore, in our series, the overall frequency of postradiation sarcomas is 46% (13 of 28 cases). If we consider only the Mayo Clinic cases, excluding the consultation cases, 11 of 16 cases had prior irradiation, and the frequency of postradiation sarcoma was 69%. This frequency in the Mayo Clinic cases can be considered separately because the history for the consultation cases may not be equally accurate, especially if we consider that in some instances in our series (Patients 6, 9, 15), as in cases reported in the literature,[16] the radiation therapy had been given at the site of fibrous dysplasia for conditions other than fibrous dysplasia itself. In such cases, the history of prior irradiation could be missed, unless this information is carefully sought. Therefore, we believe that the role of radiation therapy still needs to be emphasized in the occurrence of sarcoma in fibrous dysplasia, although sarcomas in patients with fibrous dysplasia do occur without prior radiation therapy. For these reasons, as already recommended,[1,4,21,27] radiation therapy should be avoided in the treatment of fibrous dysplasia because it is ineffective and dangerous for secondary sarcoma.

An accurate and timely diagnosis of the sarcoma is necessary for adequate treatment (that is, the same as that of the corresponding primary sarcomas). Fibrous dysplasia itself may enter into the differential diagnosis of a low-grade central osteogenic sarcoma, which may mimic both the clinical and the radiographic findings of fibrous dysplasia. From the Mayo Clinic files of more than 1200 osteosarcomas, a recent review[40] found 15 cases of low-grade central osteosarcoma. From the consultation cases, an additional 64 patients with low-grade central osteosarcoma were found. Symptoms were frequently of long duration, and the radiographic appearance was often similar to that of fibrous dysplasia. Therefore, the differential diagnosis is mainly histologic: invasion of bone marrow and periosteum by the tumor is a constant feature of low-grade osteosarcoma, and it is never observed in fibrous dysplasia located outside the jaws. Alternatively, two conditions occurring in fibrous dysplasia may clinically mimic a sarcomatous change: the first is the coexistence of a secondary aneurysmal bone cyst with fibrous dysplasia, and the second is a possible cystic degeneration of fibrous dysplasia. This last condition is especially frequent in fibrous dysplasia of the ribs, but it can be observed in other bones.[41] Extremely useful in the differential diagnosis of these two conditions are computed tomography and magnetic resonance imaging, which generally

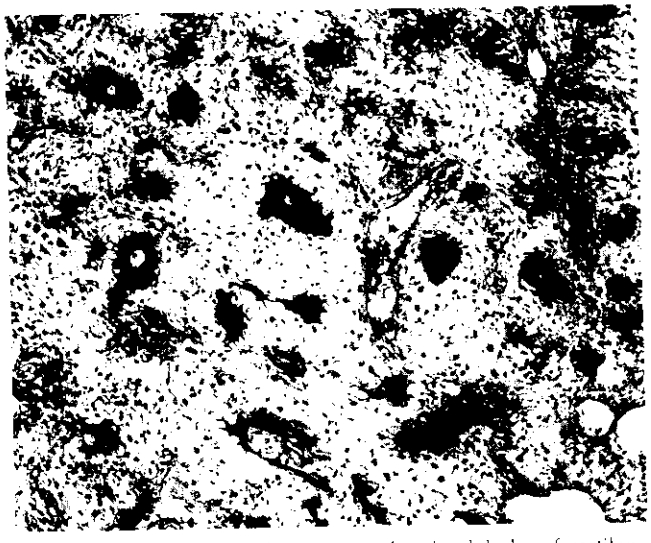

Figure 12. Clear cell chondrosarcoma, showing lobules of cartilage with central bone formation (H & E, original magnification × 100).

allow identification of fluid levels within the lesion and rule out the possibility of a malignancy.[41]

Regarding prognosis, in our series it is difficult to compare the prognosis of sarcomas in fibrous dysplasia with that of the same sarcomas in a patient without preexisting lesions, for several reasons. Patients were treated in different periods with different methods, and most of the cases were old. Moreover, as already mentioned, interpretation of the data concerning margins for the old cases was often arbitrary. Finally, there were several tumors in the jaws and several postradiation sarcomas. For these considerations, comparison of prognosis would require several different control groups for the same sarcomas equally treated and in the same sites, and such a study was not possible. We believe that these cases had basically the same prognosis as the same sarcomas not associated with fibrous dysplasia. The few patients treated more recently with adequate operation and adjuvant chemotherapy seemed to do better. If the prognosis of these sarcomas is to be improved, it is necessary to accomplish an early diagnosis of malignancy and adequate therapy.

The early recognition of a sarcoma developing in fibrous dysplasia relies mainly on the accurate clinical history: the patients almost invariably have rapidly developing symptoms, such as pain and swelling. The possibility of a sarcoma in fibrous dysplasia should be considered, and similar symptoms in a patient with fibrous dysplasia should alert the physician promptly. The most constant radiographic feature is the extension of the lesion through the bony cortex in the surrounding soft tissues. If the diagnosis is suspected, computed tomography and, in particular, magnetic resonance imaging are the best noninvasive means for early detection of a malignancy in fibrous dysplasia.

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